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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,861	03/05/2001	James R. Broach	60623CIP(50370)	4402

21874 7590 05/17/2007
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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
05/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/581,861	BROACH ET AL.	
	Examiner	Art Unit	
	Sue Liu	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/26/07.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,53,54,57,59,60 and 120-131 is/are pending in the application.

4a) Of the above claim(s) 123-131 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,53,54,57,59,60 and 120-122 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

JON EPPERSON
PRIMARY EXAMINER

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 2-52, 55-56, 58, and 61-119 have been canceled as filed on 5/8/06.

Claims 123-131 have been added as filed on 2/26/07.

Claims 1, 53, 54, 57, 59, 60, and 120-131 are presently pending.

Claims 123-131 have been withdrawn.

Claims 1, 53, 54, 57, 59, 60, and 120-122 are being examined in this application.

Request for Interview

2. Applicants have requested an interview before the issuing of a final office action in the Reply (2/26/07; p. 23). A curtsey phone call was made on 5/9/07 by the examiner and SPE (James Schultz) to inform applicants' representatives that an interview would not be granted before the issuing of a Final Office action due to the time constraint. It is also noted that applicants have filed claim amendments and response to the First Office action, and it is unlikely that an interview would help to advance prosecution of the instant application. However, applicants were invited to request an interview after the issue of the Final Office action.

Election/Restrictions

3. Applicant's election of the *"single disclosed species"* of the human bradykinin receptor as the heterologous G protein coupled receptor and the sandwich chimera Galphaq(1-11)-GPA1 (6-467)-Galpaq(355-359) of Example 12, which substitutes both the N and C terminus of GPA1

with 1st and 2nd heterologous subunits derived from the same source, in the reply filed on 8/20/04 is as previously acknowledged.

4. The newly added claim 123 reciting various species of "heterologous G protein-coupled receptor", which none of the listed receptor reads on the original elected species of "human bradykinin receptor". Thus, claim 123 is withdrawn due to non-elected species.

5. Newly submitted claims 124-131 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: As applicants have pointed out (Reply, p. 8, para 2), the newly added claims 124-131 correspond to the claims of the original non-elected inventions (Groups 4 and 5; Claims 27-29 and 41-43). The originally presented groups of inventions have been shown to not share a common special technical feature and a lack of unity was demonstrated (see Restriction Requirement mailed 7/21/04).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 124-131 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. This application contains claims 124-131 drawn to an invention nonelected with traverse in the reply filed on 8/20/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (09/581,861 filed 3/5/2001) claims priority under:

a. 371 of PCT/US98/21168 (filed 10/07/98); and

b. CIP of 08/946,298 (filed 10/7/97) as well as earlier applications.

Upon review of the two above cited documents, the presently claimed (and elected invention) finds disclosure support in the PCT/US98/21168 application (filed 10/07/98) BUT not the 08/946,298 (filed 10/7/97) application which lacks direct or exemplary support for the presently claimed scope of claims e.g. the substitution GPA variants as well as the sandwich chimeras. Accordingly, the present elected claims are granted the filing date of the PCT application (e.g. **10/7/98**) for purposes of prior art.

Oath/Declaration

8. The oath or declaration filed on 3/5/01 is acknowledged. The previous set forth objection to the Oath/Declaration has been withdrawn.

Drawings

9. The drawings/figures are objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R.§§1.821-1.825 will be published as part of the patent. Applicants should amend the specification to delete any Figures which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable format (i.e. as SEQ ID NO:'s) and should further amend the specification accordingly to reflect the replacement of the Figure by the appropriate SEQ ID NO:.

Appropriate correction is required.

10. Contrary to applicant's assertion, the sequences listed in the instant Figure 1 does constitute as "sequence listings" (i.e. lists of sequences). Applicants are requested to either delete the said Figure, OR identify the listed sequences with their corresponding SEQ ID Nos in the "BRIEF DESCRIPTION OF THE FIGURES AND TABLES" of the instant specification, in accordance with the "Sequence Rule" (see "Sequence Rule Compliance" under "Specification" of the instant Office action).

Specification

Sequence Rule Compliance

11. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2).

However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reason(s) below:

The instant disclosure recites lists of sequences in the drawings, which are not identified by their corresponding SEQ ID Nos in the "BRIEF DESCRIPTION OF THE FIGURES AND TABLES" of the instant specification. Applicants are requested to amend the instant specification and claims accordingly.

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement Rejection

14. Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating recombinant yeast cells comprising certain heterologous G-protein coupled receptors (GPCR) (e.g. C5a, FPRL, ML1aR etc.; p.91 and 104 of the instant specification) with certain GPA1 chimeric G-protein subunit,

does not reasonably provide enablement for any combination of GPCR and mutant G-protein alpha subunit within any recombinant yeast cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06, at p. 5.

Discussion and Answer to Argument

15. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants assert the structure and/or function of G-protein coupled receptors (GPCRs) are well known at the time of the filing. (Reply, pp. 10-12).

The instant claims are not drawn only to a product of GPCRs, rather the claims are drawn to a combination of a GPCR and a G protein that are associated together to produce signal transduction activities. Applicant's discussion of how well-known the family of GPCRs (pp. 10-13) do not indicate the claimed combinations of GPCRs and G proteins are well-known.

Applicants also argue "G protein subunits and G protein coupled receptors interact in a predictable fashion". (Reply, pp. 13-15).

As pointed out by applicants, "the proper test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation" (Reply, p. 13, last para).

Thus, the instant specification (coupled with information known in the art) must provide sufficient disclosure to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." The instant claims encompass any yeast cell comprising any combination of GPCR and chimeric G proteins. The instant claims also dictate that the combination of GPCR and chimeric G proteins must function properly to produce the proper signal transduction activity.

Therefore, one of skilled in the art must be able to make and use yeast cells comprising GPCRs and chimeric G proteins that can properly interact with each other to produce the claimed signal transduction activity.

Neither the instant specification nor the art teach all possible combination of GPCR and Gpa1 (including various mutants) that would produce the proper signal transduction activity. The instant specification or the art also does not provide guidance as to the specific (core) structural requirement for both the claimed genus of GPCR and the claimed genus of chimeric G protein that can be properly combined to produce the required signal transduction activity. For example, it is not clear what core sequences are required for the Gpa1 mutants to properly interact with any of the claimed GPCRs (of various sequences and structures).

As discussed in the previous rejection, there are examples of certain Gpa1 (including mutants) that are not compatible with certain GPCRs (Office action; mailed 8/24/06; pp. 8-9). Applicants have not demonstrate how one skilled in the art can predict which chimeric G protein would be compatible with which GPCR using the information provided in the instant specification and art.

Applicants also argue that the cited references (examples of incompatible GPCR and Gpa1 in the previous Office action) are "misplaced", because the "references merely exemplify the state of the art ***prior*** *to applicants' clamed invention." (Reply, p. 14, para 3; emphasis provided by applicants).*

Contrary to applicants' assertion, the cited references are not misplaced because they demonstrate the state of the art at the time the invention was made. One of the factors that are considered in determining enablement of an invention is "the state of **prior** art". (see MPEP 2164.01(a) and *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*)

Applicants also argue "the Federal Circuit has long held that it is not necessary for all possible embodiments of a claim to be operative in order for that claim to be enabled" and citing the Altas Powder case. (Reply, p. 15, para 1). Applicants also argue it's "routine methods identify compatible G protein-coupled receptors and sandwich chimeric G proteins". (Reply, pp. 15-17).

It is noted the "*Altas Powder*" (citation omitted) case further states "Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid". That is to say "claims reading on significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative". (see MPEP 2164.08(b)).

As discussed above and previously, several "inoperative" examples were cited in the previous office action as well as disclosed in the instant specification. Because the instant specification does not provide guidance as to which GPCR(s) would not be compatible with which chimeric G protein(s), it is likely that the "inoperative" combinations (of GPCR and Gpa1) represent "significant numbers of inoperative embodiments", and rendering the claims non-enabled for its full scope.

The instant claims are drawn to any heterologous G protein coupled receptor, which encompasses numerous different proteins that share partial common structure (as evidence by the instant specification). The instant claims are also drawn to any chimeric G protein subunit that is comprised of any Gpa1 mutant and any other heterologous G protein subunit (mutant or wildtype), which also encompasses numerous (hundreds and thousands) different proteins that may or may not share a common core structure. Potentially, there could be hundreds and thousands of possible combinations of GPCRs and chimeric G proteins.

As discussed in the previous Office action, the level of skills required to conduct the experiments are high. Thus, it would take "undue experimentation" to screen the numerous possible combinations of GPCRs and chimeric G proteins to determine which combination would produce the working combination and elicit the proper signal transduction activity.

Contrary to applicant's assertion that the screening experiments are "standard" techniques (Reply, p. 16), the screening experimentation for compatible GPCR and G proteins are "undue".

Because the instant specification does not provide guidance on the structural requirements (e.g. sequence or protein folding structure) for both GPCR and chimeric G proteins

that would be compatible to elicit the required signal transduction activity, it would take undue experimentation for one of skilled in the art to determine which ones are compatible.

Second paragraph of 35 U.S.C. 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The previous rejection is partially maintained for the reasons of record as set forth in the Office action, mailed 8/24/06. C

Claim 1 recites the limitations "the last four C-terminal amino acids" in lines 8 and 9, and "the first five N-terminal amino acids" in line 11, "the signal transduction activity" in line 15 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim 53 recites the limitations "the last four C-terminal amino acids" in lines 8 and 9, and "the first five N-terminal amino acids" in line 11. There are insufficient antecedent bases for these limitations in the claim.

Claim 54 recites the limitations "the last five C-terminal amino acids" in line 2, and "the first five N-terminal amino acids" in line 4, "the first 11 N-terminal amino acids" in line 5 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Claim 59 recites the limitations "the last four C-terminal amino acids" in line 2, and "the first five N-terminal amino acids" in line 4 of the claim. There are insufficient antecedent bases for these limitations in the claim.

Discussion and Answer to Argument

18. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicant's argument (Reply, p. 17, para 4) over the phrase "the signal transduction activity" is persuasive, and thus the rejection over the said phrase is withdrawn.

Applicants also argue that the claim amendment would overcome the above listed rejections. (Reply, p. 17, para 3).

However, applicant's amendments to the claims are not sufficient to overcome the said rejections. The instant claims are drawn to a genus of heterologous G protein subunits, which encompass various G protein subunits (including both mutants and wildtype). The instant specification does not provide specific amino acid sequence for each of the G protein subunits within the claimed genus. One of ordinary skill in the art would not be able to apprise the metes and bounds of the claimed range of mutations (or chimeric G proteins).

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Pausch

20. Claims 1, 59, 121 and 122 are rejected under 35 U.S.C. 102(b) as being anticipated by Pausch et al. WO 95/21925 (8/95 ; cited in previous Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Fowlkes

21. Claims 1, 53, 59, and 120-122 are rejected under 35 U.S.C. 102(b) as being anticipated by Fowlkes et al. WO 94/23025(10/94; cited in previous an Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Discussion and Answer to Argument

22. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants have traversed all the rejections under 35 USC 102 (b) together (Reply, p. 18+). Thus, applicant's traversal over all the prior art under 35 USC 102 (b) is addressed together.

Applicants have pointed out that the claim rejections under 35 U.S.C. § 102 are withdrawn as set forth in the office Action mailed on July 8, 2005.

The examiner concurs with the applicant that the claim rejections under 35 U.S.C. § 102 are withdrawn, however, the said references qualifies as prior art under 35 U.S.C. § 102 as set forth in the previous Office action.

Applicants also argue that the cited references (Pausch and Fowlkes) teach a genus, and the instant claims drawn to a "species", and thus the references do not anticipate the instant claims. (Reply, p. 18).

First, the instant claims are not drawn to a specific species as asserted by the applicants. The instant claims are broadly drawn to a genus of "yeast cells", a genus of "heterologous GPCR", and a genus of "chimeric G protein subunit". The instant claims do not specifically recite a specific species (or a limited number) of GPCR, and thus the claims are not drawn to species of GPCR.

The instant claims (Claim 1) recite "a chimeric G protein subunit which comprises an endogenous Gpa1 subunit ... **at least the last four** C-terminal amino acids ... are replaced ..." and also comprises "a second heterologous G protein subunit". The recited claim language can be reasonably broadly interpreted to mean almost any "chimeric G protein subunit". Basically, the instant claims are reciting a chimeric G protein subunit that comprise any modification of Gpa1 (with at least the last four C-terminal amino acid being modified) and any other modified or unmodified G-protein subunits. The phrase "at least the last four" is reasonably broadly interpreted to mean any number greater or equal to four. Thus, contrary to applicant's assertion,

the instant claims are NOT specifically drawn to a Gpa1 subunit with only four C-terminal amino acids modification.

That is the instant claims DO NOT recite a specific chimeric G protein comprised of certain fragment of Gpa1 and a fragment of another G protein subunit. Instead, the instant claims are drawn to a "genus" of chimeric G proteins or a "range" of mutations (i.e. replacement of ≥ 4 amino acids at the Gpa1 C-terminal).

Applicants are respectively directed to MPEP 2131.02:

"A SPECIES WILL ANTICIPATE A CLAIM TO A GENUS
"A generic claim cannot be allowed to an applicant if the prior art discloses a species falling within the claimed genus." The species in that case will anticipate the genus. In re Slayter, 276 F.2d 408, 411, 125 USPQ 345, 347 (CCPA 1960); In re Gosteli, 872 F.2d 1008, 10 USPQ2d 1614 (Fed. Cir. 1989)"

Applicants are respectively directed to MPEP 2131.03:

"I. A SPECIFIC EXAMPLE IN THE PRIOR ART WHICH IS WITHIN A CLAIMED RANGE ANTICIPATES THE RANGE
"[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated' if one of them is in the prior art." Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing In re Petering, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962))"
(emphasis added).

As discussed in the previous Office action, both of the Pausch and Fowlkes references teach replacing some portion of the Gpa1 C-terminal domain with the N-terminal domain of another G-protein (i.e. a heterologous G protein subunit).

For example, as discussed in the previous Office action, the Pausch reference teaches "recombinant yeast cells comprising "chimeric G-Protein subunits" comprising GPA1 and Gα in which the chimeric is formed by fusing the amino terminal domain of yeast GPA1 and the carboxy terminal domain of a heterologous Gα (pp. 14, lines 17-20, and Claims 17 and 18 of the

reference)". In other words, the reference teaches a "species" of chimeric G protein where the C-terminal of Gpa1 was replaced, which falls within the "genus" or the "range" of "**at least** four". Thus, the reference anticipates the claimed invention.

As discussed in the previous Office action, the Fowlkes reference teaches "yeast comprising alpha chimeras composed of N-terminal yeast alpha subunits fused to at least 10, 20 or 40 C-terminal yeast amino acids (page 43-top of page 44)", which is within the scope of "**at least** the last four C-terminal amino acids" as presently claimed (e.g. Claims 1 and 53).

Applicants also state "the Examiner acknowledges that Pausch fails to describe each and every limitation of Applicants' claimed invention" and citing p. 20, ll 5-7 from the previous Office action. (Reply, p. 18).

The citation quoted by applicants are part of the discussion in the claim rejection under 35 USC 103(a). The limitation that is not taught by Pausch et al is recited in the instant claim 57, as discussed in the previous Office action (p. 20, para 3). It is noted that the instant claim 57 was not rejected under 35 USC 102(b) using the either the Pausch or the Fowlkes reference.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Pausch and Conklin

24. Claims 1, 57, 59, 121 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al WO 95/21925 (8/95 ; cited in previous an Office action mailed on 10/19/2004) and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Pausch, Conklin, and Fowlkes

25. Claims 1, 53, 57, 59, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al WO 95/21925 (8/95 ; cited in previous an Office action mailed on 10/19/2004) and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004) as applied to claims 1, 57, 59, 121 and 122 above, and further in view of Fowlkes et al. WO 94/23025(10/94; cited in previous an

Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Fowlkes and Conklin

26. Claims 1, 53, 57, 59, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004) and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Pausch, Fowlkes Conklin, and Hamm

27. Claims 1, 53, 54, 57, 59, 60, and 120-122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pausch et al (WO 95/21925; 8/95; cited in previous an Office action mailed on 10/19/2004), Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004), and Conklin et al (Molecular Pharmacology, Vol. 50(4) Oct. 1996 pages 885-890; cited in previous an Office action mailed on 10/19/2004) as applied to claims 1, 53, 57, 59, and 120-122 above, and further in view of Hamm, (J. Biol. Chem., Vol. 273(2) (Jan. 1998) pages 669-672; cited in previous an Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Discussion and Answer to Argument

28. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue because certain previously set forth rejections over previously cited references were withdrawn, it must follow that the instant claims are "non-obvious over the teachings present within a subset of these references". (Reply, pp. 19-20).

Applicant's arguments are not persuasive, because applicants have not provided substantive evidence to indicate how the cited references are not obvious over the instant claimed invention.

*Pausch and Conklin: Applicants argue "Both Pausch et al and Conklin et al, do not specifically teach replacement of amino acid residue at the N-terminus of the Chimeric G protein subunit, **as recited in clm 53**, and an endogenous yeast pheromone receptor protein is not produced in functional form, **as recited in clm 120**."(Reply, p. 20).*

However, the previously set forth "obviousness" rejection over the combination of "Pausch and Conklin" references does not include the instant claims 53 and 120. Thus, applicants' argument is irrelevant and moot.

Pausch, Conklin and Fowlkes: Applicants argue because the previous Office action (mailed 7/8/05) states that the cited references do not "teach or suggest a chimeric G proteins

... ", the obviousness rejection over the said references (Pausch, Conklin and Fowlkes) should be withdrawn. (Reply, p. 21).

However, the rejection over (Pausch, Conklin and Fowlkes) is set forth under 35 USC 103(a), and is not an anticipation rejection under 35 USC 102 (b). As long as the combination of the references renders the instantly rejected claims obvious, the rejection as set forth is proper.

In traversing this rejection, applicants have not pointed out why the rejection as set forth in the previous Office (mailed on 8/24/06) is improper, and why the combination of the references would not render the instantly rejected claims obvious.

Pausch, Conklin, Fowlkes, and Hamm: Applicants seem to argue that the Hamm reference does not teach all elements, or the Hamm reference does not provide motivation to combine. (Reply, pp. 22-23).

In responds to applicant's argument that the references do not teach all elements, applicants are respectively referred to the above discussion of the rejections under 35 USC 102 and 103, and the reason of records (e.g. previous Office action (mailed 8/24/06)). Applicants' traversal over the previous obviousness rejection is based on the analysis of the individual reference, but is not based on all the cited reference as a whole. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicants' argument that there is no motivation to combine all the references (Pausch, Conklin, Fowlkes, and Hamm), applicants' are directed to the above discussion and the reasons of record (e.g. previous Office action (mailed 8/24/06)) obviousness rejections in which the motivations for combining the references are discussed in detail, especially for mutations of the G-protein subunits in both of the N- and C-terminus.

Specifically, applicants argue that the Hamm reference does not provide motivation to modify the N-terminus of Gpa1. As discussed in the previous rejection (Office action, 8/24/06, pp. 25+), the Hamm reference specifically teaches that the N-terminal regions of the alpha subunit along with the C-terminal region of the gamma subunit are both sites of lipid modification suggesting *a site of membrane attachment* (e.g. emphasis provided: see Hamm p. 669, right column 2nd full paragraph). Additionally evidence provided by references cited by Hamm leads to the conclusion by the Hamm reference that "A larger region of the C-terminal region of the Galpha subunits, as well as the N-terminal helix, has been *implicated in receptor contact* "(emphasis provided: See Hamm p. 669, right column, penultimate paragraph). Accordingly, in contradistinction to applicant's argument, the Hamm reference does specifically teach and/or suggest that the N-terminus of G protein alpha subunits is critical to promoting heterologous receptor contact or coupling.

Applicant further argues that the Hamm reference teaches away from modifying the N-terminus.

The Examiner respectfully disagrees.

Initially, it is noted that the claimed invention broadly encompasses the linking to or replacing *at least the first five amino acids* of the N-terminus of GPA1; but would encompass the entire N-terminus.

Additionally, as pointed out in the previous set forth rejection, the Hamm reference teaches and/or suggests that the N-terminus of the alpha G-protein alpha subunit is involved in promoting heterologous receptor contact or coupling. E.g. see Abstract; page 669, especially right column; the figures, especially figures 1 and 2. More particularly the reference points to the role of the 1st N-terminal 23 amino acids of the G-protein alpha subunit. See e.g. Figure 1, but particularly figure 2 and the role of the 1st N-terminal 23 amino acids of Galpha and rhodopsin receptor.

Accordingly, applicant's claims broadly encompass operably linking and/or substituting 5 or more (e.g. the entire N-terminus) amino acids of the N-terminus. In this respect, the reference provides guidance as to linking and/or substituting of 1 or more N-terminal amino acids up to the 23rd amino acid.

In the present instance, although the Hamm reference states that the C-terminus of the alpha subunit is the best characterized receptor contact region, the reference nevertheless provides evidence (as discussed above) that implicates the N-terminus in receptor contact and membrane attachment. Accordingly, the Hamm reference provides motivation to one of ordinary skill in the art to modify the N-terminus of alpha G-protein subunit in a manner analogous to that performed on the C-terminus in accordance with the Pausch et al, Fowlkes et al, and Conklin references with a reasonable expectation of making a yeast cell comprising a chimeric G-protein

subunit and heterologous G-protein-coupled receptor which act as a "surrogate for an endogenous yeast pheromone receptor in a pheromone response pathway of the yeast cell .

Double Patenting

29. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

30. Claim 1, 53, 59 and 120-122 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,864,060 in view of Fowlkes et al (WO 94/23025; 10/94; cited in previous an Office action mailed on 10/19/2004). The previous rejection is maintained for the reasons of record as set forth in the Office action, mailed 8/24/06.

Discussion and Answer to Argument

31. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

It is noted that applicants did not specifically traverse the ODP rejection as set forth in the previous Office action. However, applicants have generally traversed all the rejections as set forth in the previous Office action. Applicant's lack of specific traversal over the ODP rejection is construed as a request to hold the rejection in abeyance until all other rejections are withdrawn.

In the interest of "compact prosecution" and expediting the prosecution of the instant application. Applicants' Reply (filed 2/26/07) has been deemed responsive to the previous Office action. However, the above said ODP rejection is still outstanding and is not being held in abeyance. Applicants are requested to fully respond to the ODP rejection in the next reply.

For future correspondence, applicants are respectively reminded to fully and specifically respond to all grounds of rejections as set forth in a previously sent Office action, in order for a Reply to be fully responsive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SL
Art Unit 1639
5/10/07

JON EPPERSON
PRIMARY EXAMINER